37. (Amended) The method of claim 34, [wherein] which further comprises avoiding an interaction between DCL and a drug that inhibits cytochrome P450 [is avoided].

38. (Amended) The method of claim 34 wherein the amount of descarboethoxyloratadine (DCL) [DCL] administered is from about 0.1 mg to less than about 10 mg per day.

39. (Amended) The method of claim 38 wherein the amount of descarboethoxyloratadine (DCL) [DCL] administered is from about 0.1 mg to less than about 5 mg per day.

40. (Amended) The method of claim 34 wherein the amount of said descarboethoxyloratadine (DCL) [DCL] or a pharmaceutically acceptable salt thereof is administered together with a pharmaceutically acceptable carrier.

REMARKS

The application is a division of Application No. 09/039,260, filed March 16, 1998, currently pending, which is a division of Application No. 08/783,393, filed January 13, 1997, now U.S. Patent No. 5,731,319, which is a division of Application No. 08/366,651, filed December 30, 1994, now U.S. Patent No. 5,595,997. As such, the application claims proper priority to December 30, 1994.

Claims 34-40 are currently pending in the application for the Examiner's review and consideration. Claims 34 and 38-40 have been amended to more clearly recite that the methods recite amounts of descarboethoxyloratadine (DCL). Claim 35 and 37 have been amended to more clearly and distinctly define the embodiment of the invention. Support for these amendments is found in the specification and claims as originally filed. No new matter has been added by this amendment. An early notice of allowance is requested so that the application may proceed to issue.

I. The Rejections Under 35 U.S.C. §112, Second Paragraph, Have Been Obviated

Claims 35-37 and 40 were rejected under 35 U.S.C. § 112, second paragraph, on page 2 of the Office Action as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants respectfully submit that the amendments to claims 35-37 and 40 render the alleged lack of antecedent basis moot. Further, Applicants believe that Examiner has mistakenly interpreted the subject matter in claim 36 as referring to the avoidance of adverse effects; this is not the case. Claim 36 further defines the human to whom the treatment is being rendered. Thus, the rejection of claim 36 is an error and Applicants request it be withdrawn.

Applicants therefore respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

II. The Rejections Under 35 U.S.C. §103(a)

Claims 34-40 were rejected under 35 U.S.C. § 103(a) as being obvious over *The MERCK MANUAL of Diagnosis and Therapy*; 1992, pp. 332-334 to Berkow *et al.* ("Berkow") in view of U.S. Patent No. 4,659,716 to Villani *et al.* ("Villani") for the reasons set forth on pages 3-4 of the Office Action. Applicants respectfully traverse this rejection.

As the Examiner is well aware, three basic criteria must be met to establish a case of *prima facie* obviousness: first, there must have been at the time of the invention a motivation to combine the references cited; second, the alleged prior art must teach or suggest all of the limitations of the claims alleged to be obvious; and third, there must have been at the time of the invention a reasonable expectation of success. MPEP § 2142. In addition, a *prima facie* case of obviousness may be rebutted by showing that the claimed invention achieves unexpected results or by showing that the art teaches away from the claimed range. MPEP § 2144.05(III).

The pending claims recite, in part, a method of treating urticaria in a human which comprises administering to a human, in need thereof, a therapeutically effective amount of descarboethoxyloratadine (DCL) or a pharmaceutically acceptable salt thereof. Applicants respectfully submit that the cited art does not disclose or suggest the claimed

invention much less provide the legally required reasonable expectation of success as discussed below.

The primary reference, Berkow, discloses that symptoms of acute urticaria usually can be relieved with oral first generation anti-histamines, such as diphenhydramine, hydroxyzine, or cyprohependine.[1] *See* Berkow, page 333. Berkow also states that "nonessential drugs" should be stopped since urticaria itself can be and is commonly caused by adverse drug actions. First, at best, Berkow only suggests that first generation histamine antagonists having anticholinergic and sedative effects (*e.g.*, diphenhydramine, hydroxyzine, and cyproheptadine) have an effect on urticaria. Berkow does not disclose or suggest the use of any second generation non-sedating antihistamines, much less DCL, as recited by the pending claims, to treat urticaria. Second, non-sedating antihistamines such as terfenadine and astemizole are known to cause certain adverse effects. In particular, they are known to cause cardiac arrhythmias. Indeed, these non-sedating antihistamines should not be coadministered with medications that inhibit cytochrome P450 activity, because drug interactions have been associated with cardiac arrhythmias.[2] *See Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th Ed. 1996, pp. 1607 (Exhibit A, enclosed herewith.) Thus, one of ordinary skill in the art would not read the suggestion in Berkow to use first generation antihistamines as a suggestion to use second generation antihistamines, which are known as a class to have different properties (*e.g.*, lack anticholinergic activity) and some of which are known to have serious potential for cardiac toxicity. Berkow's teaching of first generation antihistamines can be considered as a teaching away from second generation antihistamines. In sum, Berkow does not disclose or suggest the invention.

Villani does not remedy the deficiencies of Berkow. Villani merely discloses a class of compounds of the type: 8-(halo)-substituted-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta-[1,2-b]pyridines. *See* Col. 1, lines 17-38. Villani further discloses a pharmaceutical composition comprising 8-(halo)-substituted-6,11-dihydro-11-(4-

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[1] Such antihistamines are generally believed to be sedating, unlike second generation antihistamines. *See Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th Ed.; 1996, pp. 586-591 (Exhibit B, enclosed herewith).

[2] It should be noted that claim 37 recites a method of treating urticaria which comprises administering a therapeutically effective amount of DCL, wherein the interaction between DCL and a drug that inhibits cytochrome P450 is avoided.

piperidylidene)-5H-benzo[5,6]cyclohepta-[1,2-b]pyridines, allegedly having antihistaminic properties, and low central nervous system (CNS) activity indicative of non-sedation. Villani does not disclose or suggest the treatment of urticaria with any of its compounds.

In sum, Berkow suggests treating the symptoms of urticaria with a first generation sedating antihistamine, and Villani only discloses certain second generation antihistamines and says nothing about urticaria. Assuming a motivation to combine the cited references existed, one of ordinary skill in the art would not have been motivated to use the second generation antihistamine DCL to treat urticaria in humans much less be given a reasonable expectation that DCL would work and work without adverse effects associated with second generation antihistamines.

It is further well settled that in order to form a proper basis for a rejection under 35 U.S.C. § 103, the prior art must provide some suggestion, either explicit or implicit, of the combination that allegedly renders a claimed invention obvious. MPEP § 2142. *See also*, *In re Sernaker*, 217 USPQ 1 (Fed. Cir. 1983); *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985); *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988); *Panduit Corp. v. Denisson Manufacturing Co.*, 1 USPQ2d 1593, 1597 (Fed. Cir. 1987); *In re Nilssen*, 7 USPQ 2d 1500 (Fed. Cir. 1988); *Ex parte Dussaud*, 7 USPQ 2d 1818 (1988). Furthermore, "[t]he mere fact that references *can* be combined . . . does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP at § 2143.01.

As stated above, Berkow only discloses first generation histamine antagonists having anticholinergic and sedative effects (*e.g.*, diphenhydramine, hydroxyzine, and cyproheptadine) and states that they usually can relieve symptoms of urticaria. Berkow does not disclose or suggest non-sedating antihistamines, much less DCL, as recited by the pending claims. As there are literally hundreds of antihistamines known to those skilled in the art, it is respectfully submitted that a conclusion that Berkow suggests with a reasonable expectation of success that any or all antihistamines could be used to treat urticaria is improper. Further, a conclusion that all of the elements recited by the pending independent claims are disclosed by a combination of Berkow and Villani can only be based on impermissible hindsight, *i.e.*, on a consideration of the art without stepping "backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." MPEP at § 2142.

Thus, neither Berkow nor Villani taken alone or in combination suggest a method of treating urticaria that comprises the administration of a second generation antihistamine much less a method of using DCL specifically to treat urticaria. Further neither reference taken alone or in combination provides the required reasonable expectation of successfully arriving at the claimed invention.

Applicants therefore respectfully request that the rejection of claims 34-40 under § 103 be withdrawn.

No fee is believed due for this submission. Should any additional fees be required, however, please charge such fees to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Respectfully submitted,

Date August 23, 2000

45,479
Max Bachrach (Reg. No.)

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Enclosures

Systemic therapy with *griseofulvin* is more effective for moccasin and vesicular bullous disease, and is followed by long-term topical therapy with the azoles and allylamines. Itraconazole, fluconazole, and oral terbinafine combined with a topical azole or terbinafine may replace griseofulvin therapy in the future.

Onychomycosis. Fungal infection of the nails is most frequently caused by dermatophytes but also can be caused by molds and *Candida*. Mixed infections are common. The nail must be cultured prior to therapy, since 30% of nail problems that appear clinically to be onychomycosis are actually due to psoriasis or another dystrophic nail condition (Achten and Wanet-Rouard, 1978). Onychomycosis serves as a reservoir for dermatophytes and contributes to treatment failure and recurrence of tinea pedis.

Oral therapy is necessary for onychomycosis, although the agents currently available, griseofulvin and ketaconazole, have limited efficacy. Treatment of onychomycosis of toenails with griseofulvin for 12 to 18 months produces a cure rate of 50% and a relapse rate of 50% after 1 year (Davies *et al.*, 1967). Results with ketaconazole are equally disappointing, and there is the additional worry of hepatotoxicity. Terbinafine, itraconazole, and fluconazole offer significant potential advantages. They quickly produce high drug levels in the nail, which persist after therapy is discontinued. Additional advantages include a broader spectrum of coverage with itraconazole and fluconazole and few drug interactions with terbinafine. Cure rates of 75% and greater have been achieved with all three drugs, with a shorter duration of treatment than for standard therapy (Gupta *et al.*, 1994a, 1994b). Intermittent regimens with itraconazole (1 week per month) and fluconazole (1 day per week) are undergoing evaluation.

Antiviral Agents

The armamentarium against viral infections unfortunately remains small. The major antiviral drug, *acyclovir*, frequently is used to treat cutaneous herpes simplex, herpes zoster, and chickenpox. The approval of *famciclovir*, a prodrug of penciclovir, and the potential approval of *valacyclovir*, a prodrug of acyclovir, may decrease the length of postherpetic neuralgia in patients. Intralesional injection of interferon alfa-2b is administered for condylomata acuminata. Improvement of psoriasis in AIDS patients with oral zidovudine has been reported. These drug are discussed in Chapter 50.

ANTIHISTAMINES

Histamine is present in mast cells, basophils, and platelets. After release, histamine binds to both H_1 and H_2 receptors in cutaneous vessels, although cutaneous injection of H_1 receptor agonists causes itching, whereas injection of H_2 agonists does not. Complete blockade of H_1 receptors does not totally relieve itching, and some studies suggest that combinations of H_1 and H_2 receptor blockers may be superior to H_1 blockers alone (Bleehen *et al.*, 1987). Older H_1 receptor antagonists have some anticholinergic activity and are sedating. Newer H_1-type antihistamines (*terfenadine, astemizole,* and *loratadine*) lack anticholinergic side effects and are nonsedating, largely because they do not cross the blood-brain barrier. *Cetirizine, acrivastine,* and *temelastine* currently are undergoing review by the FDA or are in clinical trials. H_2 receptor blockers include cimetidine, ranitidine, famotidine, and nizatidine. Besides their use in combination with H_1 receptor blockers for pruritus, the H_2 receptor blockers have immunomodulating effects and have been used in children to treat warts (Orlow and Paller, 1993). Tricyclic antidepressants act on both H_1 and H_2 receptors and have been used to treat pruritus and urticaria.

Antihistamines are frequently used in dermatology to treat pruritus due to urticaria, atopic dermatitis, contact dermatitis, psoriasis, and many other conditions. The newer, nonsedating H_1 receptor blockers are as effective as older H_1 blockers such as hydroxyzine and do not cause tachyphylaxis (Monroe, 1993). Nonsedating antihistamines should not be coadministered with medications that inhibit cytochrome P450 activity, such as ketoconazole or erythromycin, because drug interactions have occasionally been associated with cardiac arrhythmias.

The pharmacology of histamine antagonists is covered in detail in Chapter 25.

TOPICAL ANTIPSORIASIS DRUGS

Psoriasis is a chronic scaling skin eruption characterized by keratinocyte hyperproliferation. It affects 1% of the population of the United States and has a genetic basis. While there is no cure, multiple therapies exist with various modes of delivery (*see* Figure 64–1). Corticosteroids (discussed previously), calcipotriene, and anthralin are topical therapies reserved for localized disease.

Calcipotriene

Calcipotriene (DOVONEX), a vitamin D analog, was approved for the topical treatment of psoriasis in 1994. Chance observation of improvement of psoriasis in an osteoporotic patient receiving an oral derivative of 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D$], the hormonally active

ticular, histamine-induced bronchospasm may involve an additional, reflex component that arises from irritation of afferent vagal nerve endings (*see* Eyre and Chand, in Ganellin and Parsons, 1982; Nadel and Barnes, 1984).

The uterus of some species contracts to histamine; in the human uterus, gravid or not, the response is negligible. Responses of intestinal muscle also vary with species and region, but the classical effect is contraction. Bladder, ureter, gallbladder, iris, and many other smooth muscle preparations are affected little or inconsistently by histamine.

Exocrine Glands. As mentioned above, histamine is an important physiological regulator of gastric acid secretion. This effect is mediated by H_2 receptors (*see* Chapter 37).

Nerve Endings: Pain, Itch, and Indirect Effects. Histamine stimulates various nerve endings. Thus, when released in the epidermis, it causes itch; in the dermis, it evokes pain, sometimes accompanied by itching. Stimulant actions on one or another type of nerve ending, including autonomic afferents and efferents, have been mentioned above as factors that contribute to the "flare" component of the triple response and to indirect effects of histamine on the bronchi and other organs. In the periphery, neuronal receptors for histamine are generally of the H_1 type (*see* Rocha e Silva, 1978; Ganellin and Parsons, 1982).

Mechanism of Action. The H_1 and H_2 receptors have been cloned and shown to belong to the superfamily of G protein–coupled receptors. H_1 receptors are coupled to phospholipase C, and their activation leads to formation of inositol-1,4,5-trisphosphate (IP_3) and diacylglycerols from phospholipids in the cell membrane; IP_3 causes a rapid release of Ca^{2+} from the endoplasmic reticulum. Diacylglycerols (and Ca^{2+}) activate protein kinase C, while Ca^{2+} activates Ca^{2+}/calmodulin-dependent protein kinases and phospholipase A_2 in the target cell to generate the characteristic response (*see* Chapter 2). H_2 receptors are linked to the stimulation of adenylyl cyclase and thus to the activation of cyclic AMP–dependent protein kinase in the target cell. In a species-dependent manner, adenosine receptors may interact with H_1 receptors. In the CNS of human beings, activation of adenosine A_1 receptors inhibits second messenger generation via H_1 receptors. A possible mechanism for this is interaction (termed *cross-talk*) between the G proteins to which the A_1 and H_1 receptors are coupled functionally (Dickenson and Hill, 1993).

In the smooth muscle of large blood vessels, bronchi, and intestine, the stimulation of H_1 receptors and the resultant IP_3-mediated release of intracellular Ca^{2+} leads to activation of the Ca^{2+}/calmodulin-dependent myosin light chain kinase. This enzyme phosphorylates the 20-kDa myosin light chain, with resultant enhancement of cross-bridge cycling and contraction (*see* Kamm and Stull, 1985; Somlyo *et al.*, 1988; Griendling and Alexander, 1990). The effects of histamine on sensory nerves also are mediated by H_1 receptors.

As mentioned above, the vasodilator effects of histamine are mediated by both H_1 and H_2 receptors that are located on different cell types in the vascular bed: H_1 receptors on the vascular endothelial cells and H_2 receptors on smooth muscle cells. Activation of H_1 receptors leads to increased intracellular Ca^{2+}, activation of phospholipase A_2, and the local production of endothelium-derived relaxing factor, which is nitric oxide (Palmer *et al.*, 1987). Nitric oxide diffuses to the smooth muscle cell, where it activates a soluble guanylyl cyclase and causes the accumulation of cyclic GMP. Stimulation of a cyclic GMP–dependent protein kinase and a decrease in intracellular Ca^{2+} are thought to be involved in the relaxation caused by this cyclic nucleotide. The activation of phospholipase A_2 in endothelial cells also leads to the formation of prostaglandins, predominantly prostacyclin (PGI_2); this vasodilator makes an important contribution to endothelium-mediated vasodilatation in some vascular beds.

The mechanism of cyclic AMP–mediated relaxation of smooth muscle is not entirely clear, but it is presumed to involve a decrease in intracellular Ca^{2+} (*see* Kamm and Stull, 1985; Taylor *et al.*, 1989). Cyclic AMP–mediated actions in the heart, mast cells, basophils, and other tissues also are understood incompletely, but the effects of histamine that are mediated by H_2 receptors obviously would be produced in the same fashion as those resulting from stimulation of beta-adrenergic receptors or other receptors that are linked to the activation of adenylyl cyclase.

Clinical Uses

The practical applications of histamine are limited to uses as a diagnostic agent. Histamine *(histamine phosphate)* is used to assess nonspecific bronchial hyperreactivity in asthmatics and as a positive control injection during allergy skin testing.

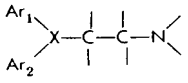
H_1-RECEPTOR ANTAGONISTS

Although antagonists that act selectively at the three types of histamine receptors have been developed, this discussion is confined to the properties and clinical uses of H_1 antagonists. Specific H_2 antagonists (*e.g.*, cimetidine, ranitidine) are used extensively in the treatment of peptic ulcers; these are discussed in Chapter 37. The properties of agonists and antagonists at H_3 receptors are discussed later in this chapter. Such agents are not yet available for clinical use.

History. Histamine-blocking activity was first detected in 1937 by Bovet and Staub in one of a series of amines with a phenolic ether function. The substance, 2-isopropyl-5-methylphenoxyethyldiethylamine, protected guinea pigs against several lethal doses of histamine, antagonized histamine-induced spasm of various smooth muscles, and lessened the symptoms of anaphylactic shock. This drug was too toxic for clinical use, but by 1944, Bovet and his colleagues had described pyrilamine maleate, which is still one of the most specific and effective histamine antagonists of this category. The discovery of the highly effective histamine antagonists diphenhydramine and tripelennamine soon followed (*see* Bovet, 1950; Ganellin, in Ganellin and Parsons, 1982). In the 1980s, nonsedating H_1-histamine-receptor antagonists were developed for treatment of allergic diseases.

By the early 1950s, many compounds with histamine-blocking activity were available to physicians, but they uniformly failed to inhibit certain responses to histamine, most conspicuously gastric acid secretion. The discovery by Black and colleagues of a new class of drugs that blocked histamine-induced gastric acid secretion provided new pharmacological tools with which to explore the functions of endogenous histamine. This discovery ushered in a major new class of therapeutic agents, the H_2 receptor antagonists, including cimetidine (TAGAMET), famotidine (PEPCID), nizatidine (AXID), and ranitidine (ZANTAC) (*see* Chapter 37).

Structure–Activity Relationship. All of the available H_1 receptor antagonists are reversible, competitive inhibitors of the interaction of histamine with H_1 receptors. Like histamine, many H_1 antagonists contain a substituted ethylamine moiety, $-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-N\diagdown$. Unlike histamine, which has a primary amino group and a single aromatic ring, most H_1 antagonists have a tertiary amino group linked by a two- or three-atom chain to two aromatic substituents and conform to the general formula:

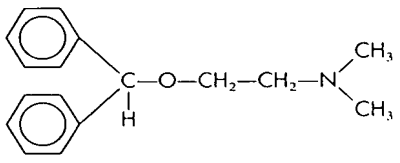


where Ar is aryl and X is a nitrogen or carbon atom or a —C—O— ether linkage to the beta-aminoethyl side chain. Sometimes the two aromatic rings are bridged, as in the tricyclic derivatives, or the ethylamine may be part of a ring structure. Other variations also are possible; for example, the piperidine H_1 antagonists *terfenadine* and *astemizole* have aromatic ring structures on either side of the carbon chain (Figure 25–2). (*See* Ganellin, in Ganellin and Parsons, 1982.)

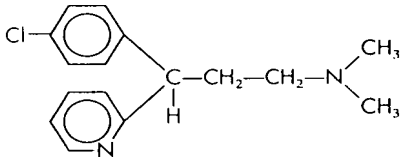
Pharmacological Properties

Most H_1 antagonists have similar pharmacological actions and therapeutic applications and can be discussed together conveniently. Their effects are largely predictable from knowledge of the responses to histamine that involve interaction with H_1 receptors.

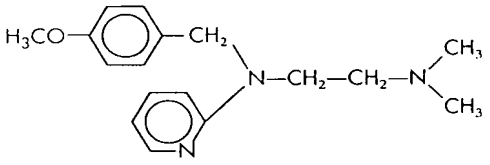
Smooth Muscle. H_1 antagonists inhibit most responses of smooth muscle to histamine. Antagonism of the constrictor action of histamine on respiratory smooth muscle is easily shown *in vivo* or *in vitro*. In guinea pigs, for example, death by asphyxia follows quite small doses of his-



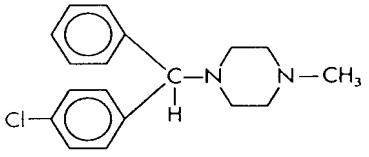
DIPHENHYDRAMINE * (an ethanolamine)



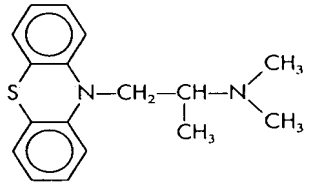
CHLORPHENIRAMINE † (an alkylamine)



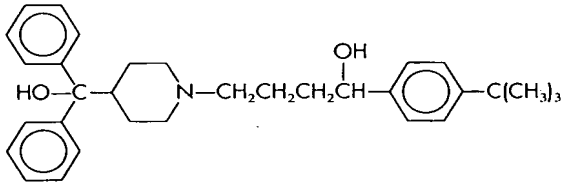
PYRILAMINE ‡ (an ethylenediamine)



CHLORCYCLIZINE § (a piperazine)



PROMETHAZINE (a phenothiazine)



TERFENADINE (a piperidine)

Figure 25–2. Representative H_1 antagonists.

*Dimenhydrinate is a combination of diphenhydramine and 8-chlorotheophylline in equal molecular proportions.
†Pheniramine is the same less Cl.
‡Tripelennamine is the same less H_3CO.
§Cyclizine is the same less Cl.

tamine, yet the animal may survive a hundred lethal doses of histamine if given an H_1 antagonist. In the same species, striking protection also is afforded against anaphylactic bronchospasm. This is not so in human beings, because allergic bronchoconstriction is caused primarily by mediators such as leukotrienes and platelet activating factor (*see* Chapter 26).

Within the vascular tree, the H_1 antagonists inhibit both the vasoconstrictor effects of histamine and, to a degree, the more rapid vasodilator effects that are mediated by H_1 receptors on endothelial cells. Residual vasodilation reflects the involvement of H_2 receptors on smooth muscle and can be suppressed only by the concurrent administration of an H_2 antagonist. Effects of the histamine antagonists on histamine-induced changes in systemic blood pressure parallel these vascular effects.

Capillary Permeability. H_1 antagonists strongly block the action of histamine that results in increased capillary permeability and formation of edema and wheal.

"Flare" and Itch. The "flare" component of the triple response and the itching caused by intradermal injection of histamine are two different manifestations of the action of histamine on nerve endings. H_1 antagonists suppress both.

Exocrine Glands. Gastric secretion is not inhibited at all by H_1 antagonists, and they suppress histamine-evoked salivary, lacrimal, and other exocrine secretions with variable responses. The atropine-like properties of many of these agents, however, may contribute to lessened secretion in cholinergically innervated glands and reduce ongoing secretion in, for example, the respiratory tree.

Immediate Hypersensitivity Reactions: Anaphylaxis and Allergy. During hypersensitivity reactions, histamine is one of many potent autacoids released (*see* above), and its relative contribution to the ensuing symptoms varies widely with species and tissue. The protection afforded by histamine antagonists obviously varies accordingly. In human beings, some phenomena, including edema formation and itch, are fairly well controlled; others, such as hypotension, are less so. Bronchoconstriction is reduced little, if at all (*see* Dahlén *et al.*, 1983).

Central Nervous System. The first-generation H_1 antagonists can both stimulate and depress the CNS. Stimulation occasionally is encountered in patients given conventional doses, who become restless, nervous, and unable to sleep. Central excitation also is a striking feature of poisoning, which not uncommonly results in convulsions, particularly in infants. Central depression, on the other hand, is the usual accompaniment of therapeutic doses of the older H_1 antagonists. Diminished alertness, slowed reaction times, and somnolence are common manifestations. Some of the H_1 antagonists are more likely to depress the CNS than others, and patients vary in their susceptibility and responses to individual drugs. The ethanolamines (*e.g.*, diphenhydramine; *see* Figure 25–2) are particularly prone to cause sedation.

The second-generation (nonsedating) H_1 antagonists (*e.g.*, terfenadine, astemizole, loratadine) are largely excluded from the brain when given in therapeutic doses, because they do not cross the blood–brain barrier appreciably (Sorkin and Heel, 1985; Krstenansky and Cluxton, 1987). Their effects on objective measures of sedation such as sleep latency, EEG, and standardized performance tests are similar to those of placebo (Simons and Simons, 1994). The lack of sedation is in contrast to the profound sedating side effects of first-generation antihistamines and may be of significant clinical benefit.

An interesting and useful property of certain H_1 antagonists is the capacity to counter motion sickness. This effect was first observed with *dimenhydrinate* and subsequently with *diphenhydramine* (the active moiety of dimenhydrinate), various piperazine derivatives, and *promethazine*. The latter drug has perhaps the strongest muscarinic blocking activity among these agents and is among the most effective of the H_1 antagonists in combating motion sickness (*see* below). Since scopolamine is the most potent drug for the prevention of motion sickness (*see* Chapter 7), it is possible that the anticholinergic properties of certain H_1 antagonists are largely responsible for this effect.

Anticholinergic Effects. Many of the first-generation H_1 antagonists tend to inhibit responses to acetylcholine that are mediated by muscarinic receptors. These atropine-like actions are sufficiently prominent in some of the drugs to be manifest during clinical usage (*see* below). The second-generation H_1 antagonists (*e.g.*, terfenadine, astemizole, loratadine) have no effect on muscarinic receptors (*see* Sorkin and Heel, 1985).

Local Anesthetic Effect. Some H_1 antagonists have local anesthetic activity, and a few are more potent than procaine. Promethazine (PHENERGAN) is especially active. However, the concentrations required for this effect are several orders higher than those that antagonize histamine.

Absorption, Fate, and Excretion. The H_1 antagonists are well absorbed from the gastrointestinal tract. Following oral administration, peak plasma concentrations are achieved in 2 to 3 hours and effects usually last 4 to 6 hours; however, some of the drugs are much longer acting (Table 25–1).

Table 25–1
Preparations and Dosage of Representative H_1-Receptor Antagonists*

CLASS AND NONPROPRIETARY NAME	TRADE NAME	DURATION OF ACTION, hours	PREPARATIONS†	SINGLE DOSE (ADULT)
First-Generation Agents				
Ethanolamines				
Carbinoxamine maleate	CARDEC;¶ others	3–6	L	4–8 mg
Clemastine fumarate	TAVIST, others	12–24	O, L	1.34–2.68 mg
Diphenhydramine hydrochloride	BENADRYL; others	4–6	O, L, I, T	25–50 mg
Dimenhydrinate	DRAMAMINE; others	4–6	O, L, I	50–100 mg
Ethylenediamines				
Pyrilamine maleate	NISAVAL	4–6	O	25–50 mg
Tripelennamine hydrochloride	PBZ	4–6	O	25–50 mg, 100 mg (sustained release)
Tripelennamine citrate	PBZ		L	37.5–75 mg
Alkylamines				
Chlorpheniramine maleate	CHLOR-TRIMETON; others	4–6	O, L, I	4 mg 8–12 mg (sustained release) 5–20 mg (injection)
Brompheniramine maleate	DIMETANE; others	4–6	O, L, I	4 mg 8–12 mg (sustained release) 5–20 (injection)
Piperazines				
Hydroxyzine hydrochloride	ATARAX; others	6–24	O, L, I	25–100 mg
Hydroxyzine pamoate	VISTARIL	6–24	O, L, I	25–100 mg
Cyclizine hydrochloride	MAREZINE	4–6	O, I	50 mg
Cyclizine lactate	MAREZINE	4–6	I	50 mg
Meclizine hydrochloride	ANTIVERT; others	12–24	O	12.5–50 mg
Phenothiazines				
Promethazine hydrochloride	PHENERGAN; others	4–6	O, L, I, S	25 mg
Second-Generation Agents				
Alkylamines				
Acrivastine	SEMPREX-D¶	6–8	O	8 mg
Piperazines				
Cetirizine hydrochloride‡		12–24	O	5–10 mg

Table 25–1 (continued)

CLASS AND NONPROPRIETARY NAME	TRADE NAME	DURATION OF ACTION, hours	PREPARATIONS†	SINGLE DOSE (ADULT)
Second-Generation Agents (cont.)				
Piperidines				
Astemizole	HISMANAL	>24	O	10 mg
Levocabastine hydrochloride	LIVOSTIN	16–24	T	One drop
Loratadine	CLARITIN	24	O	10 mg
Terfenadine	SELDANE	12–24	O	60 mg

*For a discussion of phenothiazines, *see* Chapter 18.
†Preparations are designated as follows: O, oral solids; L, oral liquids; I, injection; S, suppository; T, topical. Many H_1-receptor antagonists also are available in preparations that contain multiple drugs.
‡Cetirizine has mild sedating effects; it is not yet available in the United States.
¶Trade name drug also contains other medications.

Extensive studies of the metabolic fate of the older H_1 antagonists are limited. Diphenhydramine, given orally, reaches a maximal concentration in the blood in about 2 hours, remains at about this level for another 2 hours, and then falls exponentially with a plasma elimination half-time of about 4 hours. The drug is widely distributed throughout the body, including the CNS. Little, if any, is excreted unchanged in the urine; most appears there as metabolites. Other first-generation H_1 antagonists appear to be eliminated in much the same way (*see* reviews by Witiak and Lewis, 1978; Paton and Webster, 1985).

Information on the concentrations of these drugs achieved in the skin and mucous membranes is lacking. However, significant inhibition of "wheal-and-flare" responses to the intradermal injection of histamine or allergen may persist for 36 hours or more after treatment with some longer-acting H_1 antagonists, even when concentrations of the drugs in plasma are very low. Such results emphasize the need for flexibility in the interpretation of the recommended dosage schedules (*see* Table 25–1); less frequent dosage may suffice. Like many other drugs that are metabolized extensively, H_1 antagonists are eliminated more rapidly by children than by adults and more slowly in those with severe liver disease. H_1-receptor antagonists are among the many drugs that induce hepatic microsomal enzymes, and they may facilitate their own metabolism (*see* Paton and Webster, 1985; Simons and Simons, 1988).

The second-generation H_1 antagonists astemizole, loratadine, and terfenadine are rapidly absorbed from the gastrointestinal tract and metabolized in the liver to active metabolites by the hepatic microsomal P450 system (Simons and Simons, 1994). Consequently, metabolism of these drugs can be affected by competition for the P450 enzymes by other drugs. This alteration of metabolism can be clinically significant (*see* "Polymorphic Ventricular Tachycardia," below). Cetirizine, an active metabolite of hydroxyzine, and acrivastine also are well absorbed but primarily are excreted renally in the unmetabolized form (Brogden and McTavish, 1991; Spencer *et al.*, 1993; Barnes *et al.*, 1993).

Side Effects. ***Sedation and Other Common Adverse Effects.*** The side effect with the highest incidence in the first-generation H_1 antagonists, which is not a feature of the second-generation agents, is sedation (Carruthers *et al.*, 1978). Although sedation may be a desirable adjunct in the treatment of some patients, it may interfere with the patient's daytime activities. Concurrent ingestion of alcohol or other CNS depressants produces an additive effect that impairs motor skills (Roehrs *et al.*, 1993). Other untoward reactions referable to central actions include dizziness, tinnitus, lassitude, incoordination, fatigue, blurred vision, diplopia, euphoria, nervousness, insomnia, and tremors.

The next most frequent side effects involve the digestive tract and include loss of appetite, nausea, vomiting, epigastric distress, and constipation or diarrhea. Their incidence may be reduced by giving the drug with meals. H_1 antagonists appear to increase appetite and cause weight gain in rare patients. Other side effects that apparently are caused by the antimuscarinic actions of some of the first-generation H_1-receptor antagonists include dryness of the mouth and respiratory passages, sometimes inducing cough, urinary retention or frequency, and dysuria. These effects are not observed with second-generation H_1 antagonists, terfenadine, astemizole, and loratadine.

Polymorphic Ventricular Tachycardia. Rarely, terfenadine and astemizole cause prolongation of the QTc interval with resultant polymorphic ventricular tachycardia (*torsades de pointes*; *see* Chapter 35). The mechanism underlying terfenadine-related cases is understood and seems similar for astemizole. *Torsades de pointes* can occur when terfenadine is taken in higher-than-recommended dosages or in situations in which hepatic metabolism is impaired either by disease or by coadministration of drugs that inhibit CYP3A4, the specific cytochrome P450 thought to be responsible for terfenadine metabolism (Woosley *et al.*, 1993; Honig *et al.*, 1993). The result of overdosage or impaired metabolism is incomplete first-pass hepatic conversion of the parent drug to the carboxy metabolite. The carboxy metabolite is responsible for the clinical antihistamine actions. The parent drug, but not the metabolite, blocks delayed rectifier potassium channels, as do sotalol and quindine (*see* Chapter 35). Preexistent prolonged QTc intervals or significant hepatic dysfunction are risk factors. The drugs that most commonly inhibit CYP3A4-mediated terfenadine metabolism are the macrolide antibiotics [most notably erythromycin ethylsuccinate (E.E.S., others) and clarithromycin (BIAXIN)] and antifungal agents [most notably ketoconazole (NIZORAL) and itraconazole (SPORANOX)]. Azithromycin (ZITHROMAX) and fluconazole (DIFLUCAN), which are predominantly excreted unmetabolized in the urine, have not been associated with impaired metabolism of terfenadine. The study of drug interactions involving second-generation H_1 antagonists is evolving rapidly, and it seems certain that the list of contraindicated drugs for coadministration will increase.

Although also metabolized by CYP3A4, the second-generation H_1 antagonist loratadine does not appear to be associated with this toxicity, even with co-administration of inhibitors (Woosley and Darrow, 1994). Cetirizine and acrivistine are primarily excreted unmetabolized by the kidney and have been shown to not increase the QTc interval in normal human subjects (Sanders *et al.*, 1992; Sale *et al.*, 1994).

Mutagenicity. Results of one short-term study (Brandes *et al.*, 1994) with an unconventional mouse model indicated that melanoma and fibrosarcoma tumor lines had an increased rate of growth when injected into mice receiving certain H_1 antagonists. However, conventional studies with animals and clinical experience do not suggest carcinogenicity for H_1 receptor antagonists (Food and Drug Administration, 1994).

Other Adverse Effects. Drug allergy may develop when H_1 antagonists are given orally, but more commonly it results from topical application. Allergic dermatitis is not uncommon; other hypersensitivity reactions include drug fever and photosensitization. Hematological complications such as leukopenia, agranulocytosis, and hemolytic anemia are very rare. Teratogenic effects have been noted in response to piperazine compounds, but extensive clinical studies have not demonstrated any association between the use of such H_1 antagonists and fetal anomalies in human beings. Since H_1 antagonists interfere with skin tests for allergy, they must be withdrawn well before such tests are performed.

In acute poisoning with H_1 antagonists, their central excitatory effects constitute the greatest danger. The syndrome includes hallucinations, excitement, ataxia, incoordination, athetosis, and convulsions. Fixed, dilated pupils with a flushed face, together with sinus tachycardia, urinary retention, dry mouth, and fever, lend the syndrome a remarkable similarity to that of atropine poisoning. Terminally, there is deepening coma with cardiorespiratory collapse and death, usually within 2 to 18 hours. Treatment is along general symptomatic and supportive lines.

Available H_1 Antagonist Agents. Below are summarized the therapeutic and side effects of a number of H_1 antagonists, based on their chemical structure. Representative preparations are listed in Table 25–1.

Ethanolamines (Prototype: Diphenhydramine). The drugs in this group possess significant antimuscarinic activity and have a pronounced tendency to induce sedation. About half of those who are treated with conventional doses of these drugs experience somnolence. The incidence of gastrointestinal side effects, however, is low with this group.

Ethylenediamines (Prototype: Pyrilamine). These include some of the most specific H_1 antagonists. Although their central effects are relatively feeble, somnolence occurs in a fair proportion of patients. Gastrointestinal side effects are quite common.

Alkylamines (Prototype: Chlorpheniramine). These are among the most potent H_1 antagonists. The drugs are not so prone as some H_1 antagonists to produce drowsiness and are among the more suitable agents for daytime use; but again, a significant proportion of patients do experience sedation. Side effects involving CNS stimulation are more common in this than in other groups.

Piperazines. The oldest member of this group, *chlorcyclizine*, has a more prolonged action and produces a comparatively low incidence of drowsiness. *Hydroxyzine* is a long-acting compound that is widely used for skin allergies; its considerable central-depressant activity may contribute to its prominent antipruritic action. *Cetirizine* is an active metabolite of hydroxyzine that does not significantly penetrate the central nervous system and has less propensity to sedation. There are plans for its release in the United States in the near future. Cyclizine and meclizine have been used primarily to counter motion sickness, although promethazine and diphenhydramine (dimenhydrinate) are more effective (as is scopolamine; *see* below).

Phenothiazines (Prototype: Promethazine). Most drugs of this class are H_1 antagonists and also possess considerable anticholinergic activity. Promethazine, which has prominent sedative effects, and its many congeners are now used primarily for their antiemetic effects (*see* Chapter 38).